CHAPTER

2

Global Epidemiology of Cardiovascular Disease

GLOBAL EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) in its various forms is the leading cause of death worldwide, ranking first in both developing and developed nations. The total number of annual deaths due to CVD is more than 17 million, approximately 29% of all deaths. Furthermore, concurrent with increasing longevity throughout the world population, the burden of CVD no longer has its greater impact in the developed world. According to the most recent World Health Organizaiton (WHO) data, more than 80% of all CVD deaths occurred in developing (low and middle income) countries compared to developed (high income) countries (WHO 2009; WHO, 2010). **Figure 2.1** shows the marked excess of CVD deaths in low and middle income countries compared to high income countries (14 million versus 3 million).

Cardiovascular disease not only causes death but can also result in severe disability, particularly among those who survive a myocardial infarction or stroke. One measure of overall disease burden that is commonly used to measure the impact of *both* death and disability is *disability-adjusted life years* (DALY). The DALY extends the concept of *potential years of life lost due to premature death* (YLL) to include *years of healthy life lost due to disability* (YLD). In other words, the DALY combines mortality and morbidity into a single common measurement calculated as DALY = YLL + YLD.

Figure 2.2 depicts the burden of cardiovascular disease measured by DALY where one DALY is equivalent to the loss of one year of healthy life (WHO, 2009). Clearly, the CVD burden is higher in many of the developing nations of Asia, South America, and Africa (DALY > 5,100 per 100,000) than in the more advanced societies of North America, Europe, and Australia (DALY < 3,000 per 100,000). The composition of DALY also varies by economic region. Developing nations with high DALY rates suffer more lost years of healthy life due to premature death from CVD (60–70%) whereas developed nations lose more years of healthy life due to disability from CVD (50–60%).

SPECTRUM OF CARDIOVASCULAR DISEASE

Categorization of the pathologies underlying CVD is complex since the primary disease processes are often interdependent. Even so, more than 95% of all CVD can be categorized according to a few major pathologic conditions (Braunwald et al., 1997). Furthermore, more than 75% of deaths from CVD are attributable to either ischemic heart disease culminating in myocardial infarction or stroke culminating in cerebral infarction. These two conditions, ischemic heart disease and stroke, account for nearly one quarter of all deaths worldwide.

The approximate cause-specific global mortality rates due to the various forms of CVD are shown in **Table 2.1**. Of the 17.1 million deaths attributable to CVD every year, 7.2 million are due to ischemic (coronary) heart disease resulting in myocardial infarction (heart attack); 5.7 million are due to cerebrovascular disease (stroke), and an additional 2.2 million are due to hypertensive disease and/or congestive heart failure. The remaining deaths are due to rheumatic heart disease and inflammatory conditions (myocarditis, endocarditis, and pericarditis), aortic aneurysms, pulmonary emboli, and other cardiovascular conditions. Major diseases and conditions in

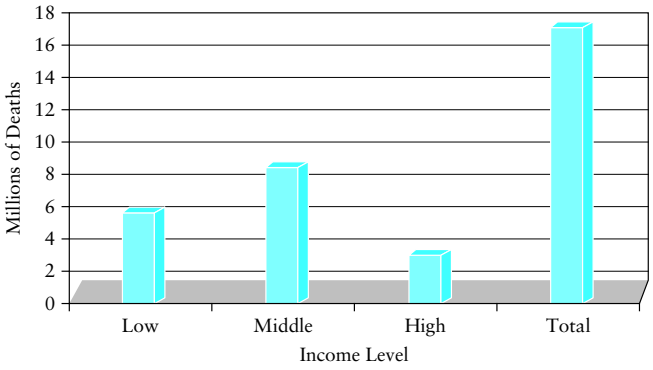

Figure 2.1 Global CVD Mortality, 2009.

Source: Data from WHO (2010). World Health Statistics 2010. World Health Organization Statistical Information System (WHOSIS), Geneva, Switzerland. Countries are grouped by national annual income per capita: Low: < $826, Middle: $826–$10,065, High: > $10,065.

the spectrum of CVD are briefly defined in the following paragraphs and separate chapters of this text are devoted to the epidemiology of these conditions.

Ischemic Heart Disease (Coronary Heart Disease) is caused by narrowing and obstruction of one or more blood vessels supplying the heart muscle itself (the myocardium). Ischemia means lack of oxygen (obviously due to the absence or lack of blood without which the heart muscle quickly dies). The catastrophic culminating event of obstructive coronary heart disease is a myocardial infarction (heart attack), which is frequently fatal. Coronary heart disease is almost always due to the presence of atherosclerotic plaque that impedes blood flow in one or more of the small caliber arteries of the heart. The development of atherosclerotic plaque (a process called atherogenesis) begins early in life and progresses over many years (usually decades) throughout the life span. Atherosclerotic

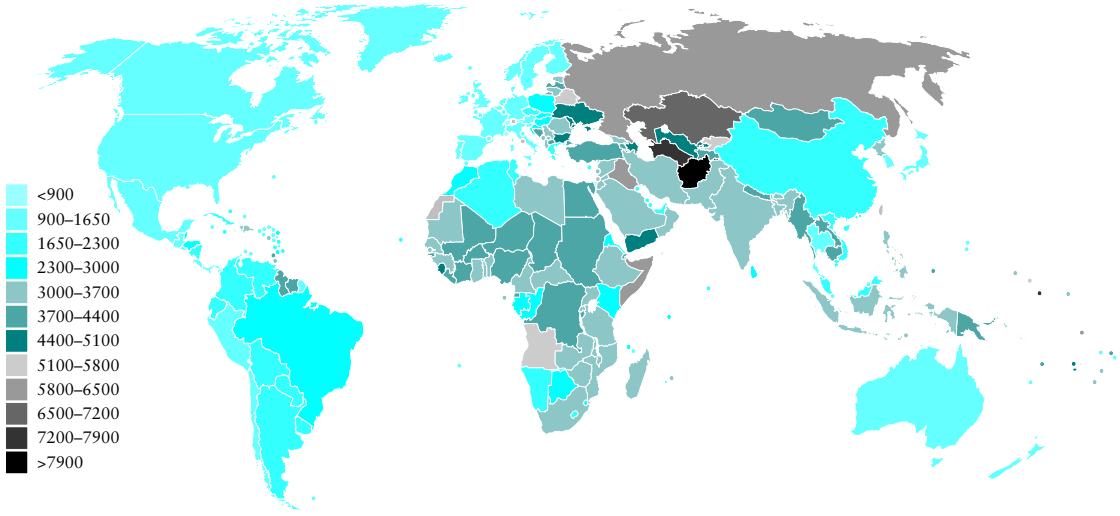

Figure 2.2 Cardiovascular Disease: Disability-Adjusted Life Years (DALY), 2004.

Source: Data from World Health Organization. The global burden of disease: 2004 update. Geneva, WHO, 2008. Available at www.who.int/evidence/bod. Age-standardized DALY from cardiovascular disease by country (per 100,000 inhabitants). Disability-adjusted life years (DALY) are rates per 100,000 people that combine Years of Life Lost (YLL) due to premature disease mortality in the population and the Years Lost due to Disability (YLD) for incident nonfatal cases of the disease (DALY = YLL + YLD). One DALY represents the loss of one year of healthy life.

Table 2.1 Relative Mortality Due to Cardiovascular Disease

• Ischemic (Coronary) Heart Disease	7.2 Million	43%
• Cerebrovascular Disease (Stroke)	5.7 Million	33%
• Congestive Heart Failure	1.2 Million	7%
• Hypertensive Heart Disease	1.0 Million	6%
• Rheumatic Heart Disease	0.3 Million	2%
• Myocarditis/Endocarditis/Pericarditis	0.2 Million	1%
• Cardiomyopathy	0.2 Million	1%
• Congenital Heart Disease	0.1 Million	1%
• Peripheral Vascular/Aortal Disease	0.1 Million	1%
• Other Conditions	1.0 Million	6%
TOTAL	17.1 Million	

Mortality rates were estimated from worldwide data published by WHO, 2004. The relative mortality due to congestive heart failure is projected from data for the US population (National Center for Health Statistics, 2006: Heron et al., 2009).

plaque may develop over time in one or more coronary arteries eventually leading to stenosis and obstruction; or plaque may develop in a larger artery upstream, e.g., the aorta, that may rupture producing plaque remnants and thrombotic fragments (blood clots) that travel to smaller vessels such as the coronary arteries where they lodge and become obstructive. The process of atherogenesis is discussed in some detail in a following section of this chapter.

Myocardial Infarction (Heart Attack) is caused by acute obstruction of a coronary artery, usually one in which blood flow is already compromised by the presence of significant atherosclerotic plaque. Most infarcts of the myocardium arise due to ischemic heart disease as a consequence of long-standing atherosclerosis. There is controversy regarding the exact sequence of events leading to a myocardial infarction, and it is likely that there is considerable variability in the process from patient to patient. One proposed scenario involves rupture of an atherosclerotic plaque followed by platelet aggregation and possibly thrombotic occlusion in key coronary arteries, e.g., the right or left anterior descending or the left circumflex artery. Albeit, the end result of a myocardial infarction is significant necrosis of the myocardium which can quickly progress to arrhythmia and sudden cardiac death.

Cerebrovascular Disease (Stroke) is caused by acute disruption of the blood supply to the brain due to either blockage (ischemic stroke) or rupture of a blood vessel (hemorrhagic stroke). As with ischemic heart disease, strokes are usually caused by atherosclerotic plaque either developing in place or dislodged from a larger (upstream) artery. Plaque rupture, platelet aggregation, and thrombotic occlusion may all be involved.

Congestive Heart Failure is the seqeula of antecedent pathologies of the cardiovascular system, primarily (but not limited) to ischemic heart disease and hypertension. This condition is defined as failure of the heart to pump blood at a rate commensurate with the requirements of the body. The life-threatening effects of congestive heart failure are congestion, edema, and hypoxia, not only in the heart itself but also in the lungs, kidneys, brain, liver, and other vital organs. Congestive heart failure is often divided into left-sided versus right-sided failure. Left-sided failure most often arises due to the combination of ischemic damage to the myocardium from coronary atherosclerosis plus peripheral hypertension requiring greater contractile force of the left ventricle to maintain cardiac output. Right-sided failure (*cor pulmonale*) can develop as a consequence of intrinsic lung disease (e.g., chronic obstructive pulmonary disease) and heightened blood pressure in the pulmonary circulation or may arise from progressive edematous changes in the lungs due to left-sided heart failure. In either case, the right ventricle encounters increased contractile resistance and is subject to hypertrophy, dilatation, and failure.

Hypertensive Heart Disease occurs when the heart continually pumps against high resistance in the peripheral circulatory system. Resistance to blood flow in the peripheral arteriolar system increases with the constriction of blood vessels (vasoconstriction). The effects of vasoconstriction and increased resistance to blood flow are measured by the blood pressure. Regulation of blood pressure is complex and involves the kidneys and other organs. Hypertension is defined as systolic blood pressure exceeding 140 mm Hg and/or diastolic blood pressure exceeding 90 mm Hg.

As the peripheral resistance to blood flow increases, the heart (particularly the left ventricle) must work harder to maintain cardiac output. This sequence leads to left ventricle hypertophy and dilatation and may cause the pooling of blood in the left ventricular chamber (left-sided congestive heart failure). If there is long-standing high blood pressure in the lungs (pulmonary hypertension), the right ventricle may undergo hypertrophy leading to right-sided congestive heart failure (*cor pulmonale*). Other factors, particularly ischemic heart disease, may contribute to and exacerbate hypertensive heart disease and congestive heart failure.

Rheumatic Heart Disease refers to damage to the heart valves and/or the myocardium caused by a persistent infection with beta hemolytic streptococcal A bacteria. The infectious process typically begins as an acute pharyngitis. Rheumatic fever develops as a sequela to the infection and involves inflammatory immune reactions in the heart and joints.

Inflammatory Heart Disease refers to inflammatory conditions of the heart other than rheumatic heart disease. Inflammatory heart disease encompasses viral myocarditis (viral infection of the myocardium), bacterial endocarditis (bacterial infection of the endocardium, the inner lining of the heart chambers), and pericarditis (infection of the pericardial membranes that surround the heart). Infectious agents may attack the myocardium directly or alternatively and may stimulate an autoimmune inflammatory response in the myocardium. A variety of viruses, bacteria, protozoa, and other microbes may be involved, especially in the immunocompromised patient.

Peripherial Artery Disease is caused by obstruction of the arteries (usually by atherosclerotic plaque) supplying the arms and legs. This condition is often a forerunner of ischemic heart disease due to atherosclerosis.

Aortic Aneurysms are abnormal dilatations of the aorta. These balloon-like outpouchings of the aorta arise primarily due to severe atherosclerosis and hypertension that produce thinning and necrosis of the artery wall. Long-standing aortic aneurysms are highly prone to rupture and discharge of blood into surrounding tissues and body cavities. Such *dissecting aortic aneurysms* are frequently fatal.

Deep Venous Thrombosis refers to obstructive blood clots in peripheral veins of the legs (veins carry blood back to the right atrium of the heart). Thrombotic material can dislodge and travel through the pulmonary arteries to the lungs, resulting in a life-threatening pulmonary embolism.

Congenital Heart Disease refers to malformation of anatomic structures (e.g., septal defects, abnormal heart valves) at birth due to genetic factors or gestational events.

DECLINING MORTALITY FROM CARDIOVASCULAR DISEASE IN DEVELOPED COUNTRIES

Cardiovascular disease is the dominating cause of death and disability throughout the industrialized world as well as in many developing nations. Nevertheless, in developed countries such as the United States, Great Britain, Australia/New Zealand, and western European nations, deaths from CVD have declined dramatically in the past several decades. Declining CVD mortality in the United States is illustrative of this trend (**Figure 2.3**). This declining

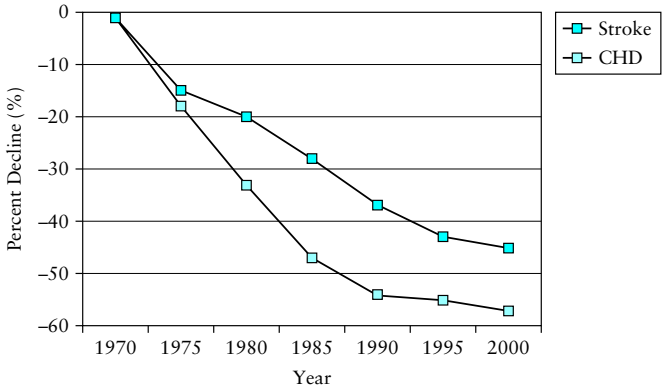

Figure 2.3 Percent Decline in CVD Mortality.

Source: Data from National Heart, Lung and Blood Institute (NHLBI, 2009). *Morbidity and Mortality: 2009 Chart Book on Cardiovascular, Lung and Blood Diseases*. National Institutes of Health, Bethesda, MD.

trend is undoubtedly due to major advances in the prevention and treatment of hypertension, ischemic heart disease, heart failure, and related conditions that predispose to fatal heart attacks and strokes. Indeed, it is estimated that more than half of the deaths due to CVD could be prevented through health promotion and disease prevention activities including cost-effective healthcare policies and individual actions to reduce exposure to major risk factors such as high blood pressure, high cholesterol, obesity, and smoking (Sanderson et al., 2007; Anand and Yusuf, 2011).

UNITED STATES MORTALITY FROM CARDIOVASCULAR DISEASE

Despite the 50% decline in deaths from ischemic heart disease and stroke during the past 40 years, CVD remains the leading cause of death in the United States (as well as most other developed nations). In 2006, CVD claimed 831,272 US lives (34.3% of all deaths) and more than 151,000 CVD victims died before reaching age 65 years. Ischemic/coronary heart disease caused 425,425 deaths in 2006 and is the single leading cause of death in the United States today (Heron et al., 2009).

Prevalent conditions among *living* Americans include high blood pressure (73.6 million), type 2 diabetes mellitus (18 million), prior myocardial infarction (8.5 million), prior stroke (6.4 million), and heart failure (5.8 million). More than one-third of these individuals have two or more forms of CVD, which synergistically increases their risk of developing a secondary catastrophic cardiovascular event, e.g., fatal myocardial infarction, stroke, or end-stage congestive heart failure (Levy, 1993).

EPIDEMIC OF CONGESTIVE HEART FAILURE IN THE UNITED STATES

One form of CVD that has markedly *increased* rather than decreased in the United States and other developed nations during the past 40 years is congestive heart failure (Bleumink et al., 2004). As shown in **Figure 2.4**, the hospitalization rate for congestive heart failure has increased more than fourfold for adults 65 years and older and more than twofold for younger adults in the United States since 1970 (National Heart, Lung and Blood Institute, 2009). This condition occurs when the heart pumps insufficient blood to meet the metabolic demands of the body. It is effectively diagnosed and monitored by measuring cardiac output as the ejection fraction of the lower heart chambers (ventricles) using electrocardiography and other imaging techniques. The normal adult range for the ejection fraction is 50–70% and congestive heart failure is indicated when the ejection fraction falls below 50%.

Many interactive factors are undoubtedly responsible for the epidemic of congestive heart failure in the United States and other developed nations. Congestive heart failure represents the end stage of a web of pathogenic events of CVD including ischemic/coronary heart disease, atherosclerosis, hypertension, type 2 diabetes, and inflammation (He et al., 2001). Indeed, improvements in the detection and treatment of these conditions have led to a significant increase in overall survival. It is estimated that more than 81 million Americans are living with two or more

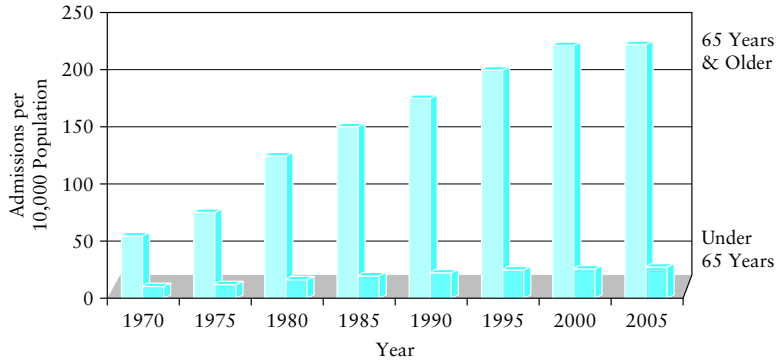

Figure 2.4 Hospitalization Rates for Congestive Heart Failure, 1970–2005, USA.

Source: Data from National Heart, Lung and Blood Institute (NHLBI, 2009). Morbidity and Mortality: 2009 Chart Book on Cardiovascular, Lung and Blood Diseases. National Institutes of Health, Bethesda, MD.

forms of CVD and as more and more patients survive CVD and live longer, their risk of developing congestive heart failure increases. Furthermore, the prevalence of certain risk factors, particularly type 2 diabetes and obesity, has increased in parallel with the rising rates of congestive heart failure.

GENDER AND ETHNIC DIFFERENCES IN CARDIOVASCULAR DISEASE IN THE UNITED STATES

Striking gender and ethnic differences are present in the rates of CVD and its spectrum of component conditions. **Figure 2.5** shows the 2006 US mortality rates for CVD and coronary/ischemic heart disease (CHD) for men and women of African American (AA) and Caucasian American (CA) ethnicity. For each stratum, coronary heart disease constitutes approximately half of the CVD mortality burden. The excess mortality among men compared to women is evident for each ethnic group, e.g., men are at an approximately 40% higher risk of dying from any form of CVD than women. The excess CVD mortality in the African American population is also striking, e.g., in gender-specific comparisons, African Americans have 38% higher CVD mortality than Caucasian Americans. These population disparities reflect not only differences in exposure to the risk factors, but also inadequacies of the healthcare system for the early detection and efficacious treatment of CVD in subpopulations of Americans (Freeman and Payne, 2000).

EPIDEMIOLOGIC TRANSITION OF CARDIOVASCULAR DISEASE

Major causes of death and disability have undergone an *epidemiologic transition* from predominantly nutritional deficiencies and infectious diseases in underdeveloped nations to chronic degenerative diseases such as cardiovascular disease, cancer, and type 2 diabetes in more advanced societies. Yusuf and colleagues divide the international patterns of cardiovascular disease into four distinct stages of the epidemiologic transition: (1) excess rheumatic heart disease and other inflammatory conditions in children and young adults in populations of sub-Saharan Africa, rural Southeast Asia, and South America; (2) excess hypertensive heart disease in young and middle-aged adults in populations of China and urban Asia; (3) rapidly increasing ischemic (coronary) heart disease and cerebrovascular disease in populations of India, Latin America, and Russia; and (4) declining cardiovascular disease among adults in populations of North America, Western Europe, Australia, and New Zealand (Yusuf et al., 2001).

While cardiovascular diseases afflict men and women of all socioeconomic classes in all geographic areas of the world, the prevalence of known CVD risk factors, and corresponding disease rates are highest and on the increase in the developing world. As a consequence, the most populous nations of the world have not yet progressed to stage 4 of the epidemiologic transition. As pointed out by Sanderson

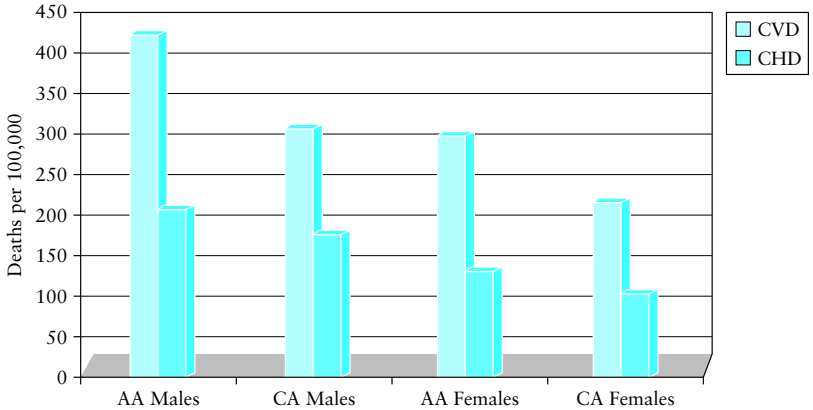

Figure 2.5 Cardiovascular Disease (CVD) and Coronary Heart Disease (CHD): USA, 2006.

Source: Data from Heron M, Oyert DL, Murphy SL, Xu J, Kochanek KD, Tejada-Vera B (2009). Deaths: Final Data for 2006. *National Vital Statistics Reports* 57, Number 14, 2009.

and colleagues in their review of the global burden of CVD:

> *"Although the mortality rate of cardiovascular diseases and prevalence of major cardiovascular risk factors has generally decreased in economically developed countries, the corresponding mortality rate, and risk prevalence has substantially increased in China, other East Asian societies and now India, which have been undergoing rapid demographic, social and, economic changes."* (Sanderson et al., 2007)

Futhermore, CVD often strikes middle-aged adults and as a result, families spiral into a cycle of poverty as they lose their primary breadwinners to death or severe disability (Anderson and Chu, 2007). Such premature death and disability reflects a virtual *pandemic* of CVD and if current trends continue, the annual death toll will approach 20 million in the developing world by the year 2020 (WHO, 2005).

RISK FACTORS FOR CARDIOVASCULAR DISEASE

The stages in the epidemiologic transition of cardiovascular diseases have occurred in response to shifts in risk factor profiles for specific cardiovascular conditions. The classical risk factors for CVD include tobacco addiction, hyperlipidemia (*high* low-density lipoprotein cholesterol and *low* high-density lipoprotein cholesterol, diabetes type 2 with hyperglycemia (increased blood glucose), hypertension, and inflammatory conditions of the heart and blood vessels. The inflammatory biomarker, C-reactive protein (CRP), has also been proven to be of value in predicting the development of CVD.

There is also convincing epidemiologic evidence that CVD risk is increased by consuming a diet high in saturated fats, being markedly overweight or obese, and maintaining a sedentary lifestyle with little physical activity. These risk factors tend to cluster in populations thereby synergistically elevating the risk to much higher levels. The time lag effect of risk factors for CVD means that the full effect of past exposure to behavioral risk factors, especially among children, will only be seen in the future. Unless preventive and management efforts are embraced worldwide, the global burden of CVD death and disease will continue to rise (MacKay and Mensah, 2004; Anderson et al., 2010). **Table 2.2** provides a listing of the major and contributing CVD risk factors, each of which is discussed in subsequent chapters.

Table 2.2 Selected Risk Factors for Cardiovascular Disease

Major Risk factors:
1. Tobacco Addiction
2. Elevated LDL Cholesterol
3. Low HDL Cholesterol
4. High Blood Pressure
5. Elevated Blood Glucose
6. Elevated C Reactive Protein
7. Obesity*
8. Physical Inactivity*
9. Dietary Factors*
Contributing Risk factors:
1. Low Socioeconomic Status*
2. Elevated Prothrombotic Factors: Fibrinogen, PAI-1
3. Markers of Infection or Inflammation
4. Elevated Homocysteine
5. Elevated Lipoprotein(a)
6. Psychological Factors (depression, anger proneness, hostility, stress, acute life-events) and Breakdown in Social Structures (loss of social support and cohesion)*

*Predisposing risk factors: A predisposing risk factor is presumed to work, at least in part, through impact on other risk factors that act directly. For example, obesity raises blood pressure, causes dyslipidemia, and increases blood glucose. It is likely that some of the contributing risk factors also have direct effects.

PAI indicates plasminogen activator inhibitor.

The global rise in CVD in developing nations reflects increases in the risk factors listed in Table 2.2: heightened consumption of westernized diets, declining physical activity levels, and increased tobacco addiction as a result of industrialization, urbanization, economic development, and market globalization. People of these nations are consuming a more energy-dense, nutrient-poor diet, and are less physically active. Imbalanced nutrition, reduced physical activity, and increased tobacco addiction are the key lifestyle factors. High blood pressure, high blood cholesterol, obesity, and type 2 diabetes are among the major biological risk factors. Unhealthy dietary practices include the high consumption of saturated fats, salt, and refined carbohydrates, and reciprocally, the low consumption of fruits and vegetables, whole grains and nuts, and certain types of unsaturated fats, e.g., omega-3 fatty acids. Futhermore, individuals in the developing world have the "double jeopardy" of increased chronic disease prevalence combined with persistently high rates of infectious diseases, leading to exceedingly high overall morbidity and mortality (Jamison et al., 2006).

PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

Primary prevention is the avoidance of known CVD risk factors. For example, individuals who never initiate the smoking habit markedly reduce their risk. Other lifestyle changes that have proven beneficial to cardiovascular health include cessation of tobacco use, aerobic exercising for at least 30 minutes daily, maintaining optimal body weight, and consuming a diet low in sodium, carbohydrates, saturated and total fats that is more weighted towards unsaturated fats, fruits, vegetables, whole grains, and omega-3 fatty acids. Compelling evidence indicates that the following strategies listed in **Table 2.3** are effective in preventing CVD and in helping manage the disease.

The most cost-effective methods of reducing CVD rates involve population-wide efforts to reduce modifiable risk factors through multiple economic and educational policies and programs. Food labeling for nutritional content; educational programs to promote decreased consumption of saturated fats, trans-fatty acids, and sodium; targeting and penalizing tobacco use; and campaigns advocating regular aerobic physical activity for weight reduction and control have proven effective in certain populations (Anderson et al., 2010).

TERTIARY PREVENTION OF CARDIOVASCULAR DISEASE

Individuals who have already experienced a cardiovascular event such as a heart attack or stroke are at high risk of suffering recurrence or death. Such individuals have numerous interventions available to them including nonpharmaceutical lifestyle modifications including regular aerobic exercising and dietary changes (e.g., restriction of salt, sugar, refined carbohydrates, and transition of the fatty acid profile to include less saturated fats and more polyunsaturated fats such as omega-3 fatty acids). Safe and effective weight reduction programs typically involve reduced caloric intake and increased fiber in the diet combined with a regular program of aerobic physical activity (Weight Control Information Network, 2010).

Pharmaceutical modalities include aspirin use, blood pressure modification, statin medication for hyperlipidemia, and specific medications to regulate blood glucose. In addition, there are a number of intensive techniques that are used in patients with cardiovascular disease, such as coronary stenting and coronary artery bypass grafting for ischemic heart disease, and thrombolytics for cerebrovascular disease.

Table 2.3 Strategies for the Prevention of Cardiovascular Disease

- Avoid smoking or using any form of tobacco.
- Maintain a healthy weight.
- Practice at least 30 minutes of aerobic physical activity daily.
- Limit energy intake from total fats and shift fat consumption away from saturated fats to unsaturated fats and towards the elimination of trans-fatty acids.
- Increase consumption of omega-3 fatty acids from fish oil or plant sources such as olive oil.
- Consume a diet high in fruits, vegetables, nuts and whole grains, and low in refined grains.
- Avoid excessively salty or sugary foods.
- Limit alcohol consumption to one drink daily.

GLOBAL PREVENTION OF CARDIOVASCULAR DISEASE

Until recently, cardiovascular disease has been largely absent from the international consciousness, overshadowed by public health concerns about HIV/AIDS and other infectious diseases. As recently as 2000, cardiovascular disease was conspicuously absent from the United Nation's Millennium Development Goals. Cardiovascular diseases are largely preventable through public health strategies and evidence-based risk factor interventions. International, national, and community programs are needed to ensure that these interventions reach the individuals most at risk. The World Health Organization has called for a global partnership of nationwide public health campaigns and high-risk intervention strategies (WHO, 2005). Organizations such as the International Cardiovascular Health Alliance (ICHA) are working in underresourced communities to establish and implement effective CVD risk factor intervention programs.

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